Pheochromocytoma

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The term “pheochromocytoma” was first proposed in 1912 by Ludwig Pick, a pathologist from Berlin in Germany. It comes from the Greek words phaios (“dark”), chroma (“color”), cytoma (“tumor”), indicating the dark staining reaction caused by the oxidation of catecholamines when exposed to chromium salts (Manger 2006, Young 2011). In humans the first pheochromocytomas (PHEO) were successfully surgically removed by César Roux in Switzerland and Charles Mayo in the US in 1926. In the following decades epinephrine (in 1939) and norepinephrine (in 1949) were isolated from PHEO tissue, and in the 1950^{ies} it was shown that patients with PHEO have elevated epinephrine and norepinephrine in plasma and urine (Manger 2006, Young 2011).
The first 2 cases of PHEO in dogs were described in 1955, interestingly also in Germany (Tamaschke 1955, Mueller et al 1955). The first PHEO in a cat was reported not until 1993 (Henry et al 1993).
For many years PHEO in dogs and cats were usually identified as an incidental finding at necropsy and ante mortem diagnoses were extremely rare. This was due to several reasons: low index of suspicion by veterinarians, the fact that clinical signs are highly variable, non-specific and often episodic, and lack of appropriate screening tests. During the last decade awareness of the potential presence of PHEO in sick animals has increased, mainly due to the routine use of abdominal ultrasonography and the frequent identification of adrenal masses. Recently, biochemical testing, i.e. measurement of catecholamines and their metabolites in urine or plasma has been introduced into veterinary medicine allowing specific diagnostic work-up (Reusch 2015).

Definition and etiopathogenesis

The WHO classification of endocrine tumors defines a PHEO as a tumor arising from catecholamine-producing chromaffin cells in the adrenal medulla. Tumors of the extra-adrenal sympathetic and parasympathetic paraganglia are classified as paragangliomas (Pacak et al 2007). The adrenal medulla, which comprises approximately one-fourth of the adrenal mass, develops during fetal life as part of the sympathetic nervous system. The latter arises from the primitive cells of the neural crest, groups of these cells migrate along the central vein and enter the adrenal cortex to form the adrenal medulla (Sjaastad et al 2010, Galac et al 2010, Fitzgerald 2011).The cells of the adrenal medulla, called pheochromocytes or chromaffin cells can be looked at as modified postganglionic sympathetic neurons lacking axons. They are stimulated by sympathetic preganglionic nerve fibers and secrete hormones into the bloodstream.
In humans many of the PHEO develop sporadically and their etiology is not understood. Recently, genetic screening revealed that a substantial percentage (20 – 30%) of patients with PHEO or paraganglioma, however, have germline mutations in genes associated with genetic disease. So far 10 genes have been identified, the 3 genes known best are: *RET* for Multiple Endocrine Neoplasia Type 2, *VHL* for von Hippel-Lindau disease and *NF1* for Neurofibromatosis Type 1 (Marini et al 2006, Maher et al 2011, Fishbein and Nathanson, 2012). It is assumed that the majority of human PHEO is benign, malignancy rates vary between 5 – 35% depending on the study. The traditional position of the WHO is to base the diagnosis of malignancy on the presence of metastasis (and not on local invasion) (Tischler et al 2006, Carlsen et al 2009). Some pathologists challenge the definition because local invasion may also be potentially lethal (Tischler et al 2006).
In dogs knowledge on potential mutation in PHEO is currently scarce. A recent study found evidence of mutations in the gene encoding succinate dehydrogenase subunit D and B (Holt et al 2014). The rate of malignant PHEO in dogs seems to be much higher than in humans, however, those comparisons depend on how malignancy is perceived. Different to human medicine either local invasion or distant metastasis usually qualifies for the definition of malignancy. Information on malignancy is mainly based on the three largest case series,

including 123 dogs with PHEO (Bouayad et al 1987, Gilson et al 1994, Barthez et al 1997). In 34% of the dogs local invasion of adjacent vessels such as vena phrenicoabdominalis, vena cava caudalis, renal vessels, adrenal vessels, hepatic veins and aorta or other tissue was found. Additional 20% of dogs had metastasis in regional lymph nodes, liver, spleen, kidneys, pancreas, lung, heart, bone and CNS. In sum, more than 50% of canine PHEO were considered malignant, a number which is often quoted today. It may, however, be that small and potentially benign PHEO go undetected and therefore the overall malignancy may be overestimated. Growth rate of PHEO is unpredictable and may range from slow to quite rapid. Dogs with PHEO may have one or several additional endocrine neoplasias, such as glucocorticoid-producing adrenocortical adenoma or carcinoma, ACTH-producing pituitary tumors, parathyroid tumor or hyperplasia, thyroid adenoma or carcinoma and insulinoma as well as non-endocrine neoplasia (Peterson et al 1982, Gilson et al 1994, Wright et al 1995, Barthez et al 1997, Thuróczy et al 1998, Beatrice et al submitted).

In the normal human medulla 80% of catecholamines is epinephrine and 20% is norepinephrine. In dogs 70% is epinephrine, 30% is norepinephrine, in cats the resp. percentages are 60% and 40% (Fitzgerald and Goldfien 2004). Epinephrine and norepinephrine are stored in intracellular vesicles, together with many other substances such as chromogranins, adrenomedullin, neuropeptide Y, vasoactive intestinal peptide, enkephalins pituitary adenylate cyclase activating polypeptide and ACTH (Thouennon et al 2010, Fitzgerald 2011). In health, catecholamine secretion increases with exercise, perceived danger, surgery, hypovolemia, hypotension, hypoglycemia and many other stressful events (Galac et al 2010, Fitzgerald 2011). The plasma half-life of catecholamines is extremely short (1 – 3 minutes). In the normal adrenal medulla and in PHEO membrane-bound COMT metabolizes epinephrine to metanephrine and norepinephrine to normetanephrine. In contrast to the catecholamines which are released only intermittently (by means of exocytosis of storage vesicles), their metabolites are constantly leaking into the circulation. This difference explains why the measurement of metanephrines (= sum of metanephrine and normetanephrine) is superior to the measurement of catecholamines in the diagnosis of PHEO (Eisenhofer 2001).
The clinical signs in patients with a PHEO can be explained by the known actions of catecholamines or, less frequently by tumor size and invasiveness. Catecholamine secretion from PHEO is highly variable with regard to relative amounts and types of catecholamines as well as to time of release (i.e. episodic versus continuous). Different to the normal medulla the majority of PHEO in humans produce more norepinephrine than epinephrine and according to preliminary results norepinephrine also seems to be the predominant catecholamine in canine PHEO (Kook et al 2007, Quante et al 2010, Salesov et al 2015). Neoplastic cells also contain various peptides, e.g. somatostatin, chromogranin A, substance P, vasoactive intestinal peptide, synaptophysin, galanin, leu-enkephalin, met-enkephalin, S 100 protein (Wilson et al 1986, Cuervo et al 1994, Sako et al 2001). It is likely that those peptides contribute to the clinical picture.

Signalement and clinical manifestations
Most dogs with PHEO are 7 years and older (mean age 11-12 years). Males and females are equally affected and there does not seem to be a breed predilection, PHEO has been described in more than 40 breeds.

The clinical manifestations related to excessive catecholamine secretion may be categorized as follows (Reusch 2015):
- Related to the cardiorespiratory system and/or hypertension: tachypnoe, dyspnoe, panting, tachycardia, arrhythmias (mostly tachyarrhythmias), collapse, pale mucus membranes, nasal-, gingival-, ocular hemorrhage, acute blindness
- Related to the neuromuscular system: weakness, anxiety, pacing, disorientation, muscle tremor, seizures

- Miscellaneous: polyuria/polydipsia, vomiting, diarrhoe, abdominal enlargement, abdominal pain.

The most common signs are weakness, lethargy, tachypnea/panting and collapse. Those signs often occur as intermittent episodes associated with intermittent catecholamine release. The episodes may occur frequently, such as several times per day or several times per week, or they may only recur after weeks to months. Their severity may range from mild to life-threatening; severity of signs may be similar each time or may progress over time. Signs may also present as acute events e.g. associated with tumor rupture, bleeding and potential catecholamine surge. The pathophysiological mechanisms for some of the clinical signs are difficult to explain resp. may be multifactorial. For instance, pu/pd may be due to excessive catecholamine release, release of other peptides from the tumor or may represent a form of tumor-induced, secondary nephrogenic diabetes insipidus. The presence of pu/pd is particularly challenging if it is the predominant sign. Together with the finding of an adrenal mass during work-up it may be mistaken as evidence for adrenal-dependent hyperadrenocorticism and the possibility of a pheochromocytoma may not be considered. Occlusion of the vena cava caudalis (partial or complete) may occur either by tumor thrombosis within the lumen or by large tumor size, both may cause ascites, hindlimb edema and distention of the caudal epigastric veins. Dogs with rupture of the PHEO are presented with acute onset of lethargy, tachypnoe, weakness or collapse, tachycardia, pale mucus membranes, prolonged capillary refill time and painful abdomen (Whittemore et al 2001, Williams and Hackner 2001). There seems to be a correlation between tumor size and severity of clinical signs. Small tumors are often an incidental finding or associated with relatively mild signs. Large tumors are often found in patients with serious clinical signs, invasion into the vena cava and/or tumor rupture.

Blood pressure

In human PHEO, hypertension occurs primarily from the secretion of norepinephrine. Interestingly, hypotension may be seen in PHEO that exclusively produce epinephrine, dopamine-producing tumors may be associated with normo- or hypotension (Fitzgerald 2011, Kitamura et al 2012). In dogs no studies investigating the relation between the type of catecholamine releases and blood pressure patterns have been performed. So far, a little more than 50% of dogs with PHEO revealed hypertension; the increase in blood pressure ranged from mild to severe with a maximum systolic blood pressure of 325 mm Hg. Hypotension was seen in one dog (Reusch et al 2010). Hypertension is not pathognomonic for PHEO and is also frequently found in hypercortisolism, which is one of the most important differential diagnosis.

Clinical pathology

Dogs with PHEO may show various abnormalities, however, changes are not consistent. The most frequent findings are: anemia (45%), increased liver enzymes, azotemia, hypercholesterolemia and hypoalbuminemia.

Diagnostic imaging

Often, a PHEO is only considered after detection of an abnormal adrenal gland on ultrasonography. Tumor size is extremely variable and ranges between a few millimeters and more than 15 centimeters. Most PHEO in dogs are unilateral, less than 10% are bilateral. No pattern of echogenicity or architecture is specific for pheochromocytomas, other adrenal masses e.g. cortisol-producing tumors may look alike (Besso et al 1997, Rosenstein 2000). Recent studies suggest, that contrast-enhanced ultrasonography have some potential to differentiate between the different types of adrenal tumors (Pey et al 2014, Bargellini et al 2016). CT has several advantages over ultrasonography. It may be particular useful in patients in which the adrenal gland is difficult to visualize (e.g. in large breed or obese dogs). It also allows a more precise and complete evaluation of tumor size, shape and architecture. Most important, contrast-enhanced CT is superior to ultrasonography to detect vascular invasion. The sensitivity and specificity of contrast-enhanced CT for vascular invasion compared to surgery or pathology was 92% and 100%, respectively. CT also correctly

identified invasion into hypaxial and epaxial musculature (Schultz et al 2009). MRI may be even superior to CT to ascertain vascular invasion due to superior resolution and contrast and it may also be more accurate to determine the exact extent of a tumor thrombus in the vena cava. Attempts to differentiate adrenal tumor types by means of CT lead to different results. Gregori et al (2015) reported that a reliable differentiation is not possible due to overlapping characteristics between tumor types; Yoshida et al (2016) suggest that differentiation is possible based on triple-phase CT findings.

Fine Needle-Aspiration and Biopsy
In humans suspected PHEO is considered to be a contraindication for FNA/biopsy and a PHEO has to be biochemically excluded prior to FNA/biopsy (Terzolo et al 2011, Bednarczuk et al 2016). FNA of PHEO has been reported in a small number of dogs and a cat (Chun et al 1997, Rosenstein 2000, Spall et al 2011). So far, no complications have been seen, however, this does not exlude the possibility of complications if performed in larger case series. In a recent study accuracy in differentiating PHEO from adrenocortical tumors by means of cytology was high (Bertazzolo et al 2014).

Biochemical testing
In humans, diagnosis of pheochromocytoma is mainly based on biochemical detection of excessive amounts of catecholamines (epinephrine, norepinephrine) and their metabolites (metanephrine, normetanephrine) in 24-h urine or in plasma. Although the question which test (urine or plasma) is best, is still somewhat controversial, plasma metanephrines tended to be recommended increasingly as test of choice. In dogs evaluation of those biomarkers for the diagnosis of pheochromocytoma has started only a few years ago. Urinary normetanephrine to creatinine ratio was shown to be the parameter, which differentiated dogs with pheochromocytoma best from healthy dogs and dogs with hypercortisolism (Kook et al 2007, Quante et al 2010). We are currently using a cut-off value of urinary normetanephrine:creatinine ratio of 4 times of normal as being diagnostic for pheochromocytoma. The plasma-test was recently investigated in dogs and plasma normetanephrine was found to be superior to plasma metanephrine for the diagnosis of PHEO (Gostelow et al 2013). Comparison of the urine and plasma test showed that discrimination of dogs with PHEO from dogs with other (adrenal) diseases was superior with urinary and plasma normetanephrine compared to urinary and plasma metanephrine. The differences between the urinary and the plasma tests were, however, small (Salesov et al 2015). Sample collection and urine processing are subject to certain conditions, such as acidification, light protection, cooled or frozen storage. Close collaboration with the laboratory is therefore necessary.

Treatment
Pheochromocytomas should be considered malignant tumors in dogs. Tumor growth is unpredictable and the risk of invasion into vessels (most often into the vena cava) and into surrounding tissues is high. Adrenalectomy is the treatment of choice and should be performed as soon as possible after diagnosis. The exceptions are very old and debilitated dogs, dogs in which the tumor is considered to be unresectable due to massive local invasion and dogs with serious concurrent diseases. The effect of preoperative treatment on anesthetic complications, surgical outcome and survival has so far only been investigated in a single study (Herrera et al 2008). Mortality rate was significantly lower in the treated group compared to the untreated group (13% versus 48%). Dogs pretreated with phenoxybenzamine were 6 times more likely to survive adrenalectomy. Currently our starting dose starting dose is 0.25 mg/kg BID, which is increased stepwise every 2 – 3 days until a final dose of approximately 1 mg/kg BID is reached. Surgery is scheduled approximately 2 weeks after the start of treatment. The last dose of phenoxybenzamine is given in the evening prior to surgery. In case of tachycardia or tachyarrhythmia, a β-blocker may be added (e.g. atenolol 0.2-1.0 mg/kg PO q 12 – 24h), however, only if the dog has received phenoxybenzamine for several days. Surgical removal of a pheochromocytoma is a high-

risk procedure and should only be performed by an experienced surgeon-anesthesiologist team. Close postoperative monitoring (best in an ICU) is mandatory.

Prognosis

Dogs that survive the immediate perioperative period and do not suffer from metastatic disease can live for several years. In dogs treated with phenoxybenzamine without subsequent adrenalectomy survival for more than a year has been seen.

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